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Venetoclax Fact Sheet

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Generic Name: Venetoclax

Synonyms: ABT-199, GDC-0199, RG7601

Trade Name(s): Venclexta™, Venclexto™, Venclyxto™

Drug Type:
Venetoclax is a targeted therapy, an antineoplastic agent, and a BCL-2 (B-cell lymphoma-2) inhibitor (for a more detailed explanation, see **How Does Venetoclax Work** below). To learn more about targeted therapies and pathway inhibitors, go to www.iwmf.com/system/files/TargetedTherapies-PathwayInhibitors-English.pdf for the IWMF Treatment Guide that also includes an explanation of ibrutinib, a BTK inhibitor.

How Venetoclax Works, and What Conditions Are Treated by This Drug:
Each type of targeted therapy is a little different, but all interfere with the ability of the cancer cell to grow, divide, repair, die, and/or communicate with other cells. Researchers identify specific features of cancer cells that are different from normal cells. This information is used to create a targeted therapy that attacks the cancer cells without damaging the normal cells, thus leading to fewer side effects. Venetoclax is a targeted therapy that restores and promotes apoptosis, a common way by which normal cells die. This programmed cell death involves an ordered sequence of biochemical events that result in cell changes (e.g. cell shrinkage, nuclear fragmentation, etc.) leading to eventual death of tumor cells in patients with WM. Venetoclax is a small molecule that can get into the cell and bind to B-cell lymphoma-2 (BCL-2), an anti-apoptotic protein, thus restoring apoptosis (death) of the cancer cell. Another way to look at this is that venetoclax blocks an important pathway promoting cell survival in tumor cells that overexpress BCL-2, so venetoclax causes tumor cells to die (pro-apoptosis).

Several studies have demonstrated that BCL-2 is overexpressed in both B-cells and plasma cells in WM patients in comparison to healthy patients. Furthermore, this overexpression of BCL-2 in samples of patients with WM happens regardless of MYD88 or CXCR4 mutation status, suggesting an independent pathophysiologic mechanism. This is being investigated with IWMF research funding.

Venetoclax has recently gained US Food and Drug Administration (FDA) approval for the treatment of patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). In late 2018, the FDA gave approval for the drug to be used in patients with acute myeloid leukemia (AML) in combination with other treatments for those who were newly diagnosed, age 75 years or older, or who have other diagnoses that preclude use of intensive first-line chemotherapy. It should be noted that if a drug has been approved for one use, physicians may elect to use this same drug for other problems if they believe it may be helpful. This is called using a drug "off-label," and clinical trials are ongoing with venetoclax alone and in combination with ibrutinib for patients with WM. In one study of patients with non-Hodgkin lymphoma (NHL), three of four patients with WM experienced a response, including a complete response in one patient. Another ongoing clinical trial on venetoclax in patients with relapsed/refractory WM has thus far shown that the therapy is well tolerated and produces high levels of response in patients with symptomatic, previously treated WM, including patients previously exposed to ibrutinib. There is laboratory evidence that the combination of ibrutinib, a BTK inhibitor, and venetoclax, a BCL-2 inhibitor is synergistic, in that the combination kills cells in a more efficient manner than either drug alone. A future clinical trial will be administering ibrutinib and venetoclax concurrently for two years, after which treatment will be stopped to determine the depth and duration of the response, as well as long-term side effects.

Special Considerations Regarding Venetoclax:
Many treatments used for WM, such as rituximab, bortezomib, carfilzomib, and bendamustine, do not have formal FDA approval for WM. However, the use of these therapies is supported by prospective data, fully vetted, published in peer-reviewed journals, and included as part of the National Comprehensive Cancer Network® (NCCN®)

guidelines and the International Waldenstrom's Macroglobulinemia Workshop consensus panel guidelines. Venetoclax, while promising, has not yet achieved such a status, and trials with patients who have WM are ongoing.

In 2019, the FDA issued a warning to health care professionals and clinical investigators about the risks associated with the investigational use of venetoclax in patients with multiple myeloma, following a review of clinical trials data that showed an increased risk of death among patients treated with venetoclax in combination with bortezomib. On the other hand, in an unpublished, multicenter, prospective phase II study of single agent venetoclax in patients with previously treated WM, the conclusion was that venetoclax is a safe and effective treatment option for such patients with WM.

How Venetoclax is Given:
Venetoclax is a tablet, taken by mouth, with a peak concentration at 5-8 hours after ingestion. These tablets should be swallowed whole once daily with water at mealtimes, as food increases bioavailability. The dose of venetoclax is administered in increasing doses over a matter of weeks to minimize potential side effects. Venetoclax is supplied as 10 mg, 50 mg, and 100 mg tablets. For initiation and dose escalation (ramp-up), venetoclax tablets are available as a 28-day starting pack containing four blister cards in a dose-specific compliance configuration. For maintenance doses, venetoclax tablets are supplied as weekly blister cards, unit dose blisters, or in bulk bottles. The tablets should not be crushed, cut, or dissolved in water, as this may reduce the venetoclax plasma concentration by up to 50%. They should be stored at room temperature. The dosage should not be changed by the patient, nor stopped. The dose should be taken at approximately the same time each day. If a dose is missed by less than 8 hours, take the missed dose of venetoclax right away, then take the next dose as usual. If a dose of venetoclax has been missed and it has been more than 8 hours, wait (don't take the venetoclax) and take the next dose of venetoclax at the usual time. Do not take more than one dose of venetoclax at one time. Call your health care professional right away if too much is taken at one time. **Do not drink grapefruit juice, eat grapefruit, Seville oranges (often used in marmalades), or starfruit while you are taking venetoclax. These foods may increase the amount of venetoclax in your**

blood. Other drug interactions include azole antifungals, conivaptan, clarithromycin, protease inhibitors, erythromycin, ciprofloxacin, diltiazem, dronedarone, verapamil, amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor, rifampin, carbamazepine, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, nafcillin, everolimus, and sirolimus. These drugs should not be taken concurrently with venetoclax. If warfarin is used concurrently with venetoclax, then it is recommended to increase the frequency of international normalized ratio (INR) monitoring for increased bleeding or other toxicity due to the warfarin. If venetoclax must be taken concurrently with digoxin, then the digoxin should be taken at least 6 hours before the venetoclax.

The amount of venetoclax that is prescribed depends on many factors, including your general health, other health problems, your absolute neutrophil count (ANC), or other drugs you are taking. Your doctor will determine your dose and schedule.

Venetoclax Side Effects:
The side effects of venetoclax and their severity depend on how much of the drug is given. High doses may produce more severe side effects. Most people will not experience all the side effects listed. Side effects are often predictable in terms of their onset, duration, and severity. They are almost always reversible and will go away after therapy is stopped. There is no relationship between the presence of side effects and the effectiveness of the medication.

The following side effects are common (occurring in greater than 30% of patients) in patients taking venetoclax: low white blood cell counts which increases the risk of infection, such as pneumonia, blood infection (sepsis), diarrhea, and nausea.
The following are less common side effects (occurring in about 10-29% of patients): anemia, low platelets (increases risk of bleeding), upper respiratory tract infections (cold symptoms), fatigue, high or low potassium in the blood, fever, vomiting, headaches, high phosphate in the blood, constipation, cough, swelling, back pain, pyrexia (raised body temperature or fever), and pneumonia.

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Tumor Lysis Syndrome is a serious, but rare, side effect of venetoclax that usually occurs within 24-48 hours of the initiation of therapy and may occur because of treatment. With treatment, large amounts of cancerous cells are rapidly killed. These cells release uric acid, potassium, and phosphorous into the bloodstream and can lead to kidney failure. Care must be taken to prevent tumor lysis syndrome. While taking venetoclax, **drink at least two to three quarts of fluid every 24 hours, particularly the 48 hours before the first dose, on the day of the first dose, and anytime the dose is increased, unless instructed otherwise by the health care team. It is important that the health care provider knows immediately if you are unable to urinate or have unusual symptoms.**

When to Contact Your Doctor or Health Care Provider:
Contact your doctor or health care provider immediately, day or night, if you should experience any of the following symptoms: fever of 100.5° F (38° C) or higher or chills (both are possible signs of infection).

Contact your health care provider within 24 hours of noticing any of the following symptoms: nausea (interferes with ability to eat and unrelieved with prescribed medications), vomiting, diarrhea (4-6 episodes in a 24 hour period), unable to eat (from causes other than nausea) or drink for 24 hours or have signs of dehydration: tiredness, thirst, dry mouth, dark and decreased amount of urine, dizziness, whites of your eyes turn yellow, signs of infection (cough without mucous, nasal drainage, burning with urination, redness or swelling, pus formation at the site of an injury or incision), fatigue that interferes with activities of daily living (showering, bathing, making meals, etc.), swelling, any signs of unusual bleeding or bruising, black, tarry, or bloody stools, blood in your urine, or heavy menstrual bleeding.

Before starting venetoclax treatment, make sure your doctor knows about any other medications being taken. Do not receive any kind of immunization or vaccination while on venetoclax without the doctor's approval. The immune response to vaccines may be diminished by venetoclax. Live attenuated vaccines should not be administered prior to, during, or after treatment until B-cell recovery has occurred due to a risk of enhanced

vaccine adverse effects. The vaccinations may be less effective. For both men and women: Use contraceptives and do not conceive a child (get pregnant) while taking venetoclax, as it may be harmful to the fetus. Barrier methods of contraception, such as condoms, are recommended during treatment and at least one month after treatment. Discuss with your doctor when it is safe to become pregnant or conceive a child after therapy. Do not breastfeed while taking this medication due to potential secretion into breast milk. Venetoclax may cause fertility problems in males. This may affect the ability to father a child. Talk to your health care provider if there are concerns about fertility. Always inform your health care provider if you experience any unusual symptoms.

Self-Care Tips While Taking Venetoclax:
There may be an increased risk of infection, so try to avoid crowds or people with colds and report fever or any other signs of infection immediately to your health care provider. Wash your hands often. Do not touch your eyes or the inside of your nose unless you have just washed your hands and have not touched anything else in the meantime.

If nausea becomes a problem, take anti-nausea medications, as prescribed by your health care team, and eat small, frequent meals. Sucking on lozenges and chewing gum may also help.

Contact your medical team before scheduling dental appointments or procedures.

Use an electric razor to minimize bleeding. Avoid contact sports or activities that could cause injury.

Avoid sun exposure. Wear SPF 15 (or higher) sun block and protective clothing. Get plenty of rest and maintain good nutrition. Discuss all symptoms or side effects with your health care team. They can prescribe medications and /or offer other suggestions that are effective in managing such problems.

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Monitoring and Testing While Taking Venetoclax:
While taking venetoclax your medical team will monitor side effects and check response to therapy. Periodic blood work will be obtained to monitor the complete blood count (CBC), as well as the function of other organs, such as kidneys and liver.

Venetoclax is not FDA-approved and not NCCN® or IWWM consensus panel-endorsed as a treatment option for WM. There is no supportive prospective data that is fully vetted and published in peer reviewed journals, and very little is known about the long-term efficacy or the toxicity of venetoclax in WM. Moreover, at this time there are no answers to questions that might arise about these issues. However, recent positive results in unpublished clinical trials with patients who have WM demonstrate the potential for venetoclax to become a key therapy for patients with WM.

NOTE: The information in this fact sheet is intended to be helpful and educational, but it does not constitute an endorsement by the IWMF and is not meant to be a substitute for professional medical advice. The IWMF acknowledges Dr. Jorge J. Castillo, Dana-Farber Cancer Institute, for his review of this Fact Sheet.

This Venetoclax Fact Sheet was made possible with funding from the International Waldenstrom's Macroglobulinemia Foundation through donations from the IWMF community of patients and caregivers. Please consider donating to the IWMF at www.iwmf.com

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